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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,183	ULMANN ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2008 and 30 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,11,14,24-28,34,40,46,49-51,53,57,59,62,64-67 and 74-76* is/are pending in the application.

4a) Of the above claim(s) *1-3,11,14,24-28,34,40,46,49,51,53,57,59 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50,64-67 and 74-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9 June 2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' response of 9 June 2008 and 30 July 2009 is acknowledged. Claim 50 has been amended and the amendment made of record. Claims 64-67 and 74-76 are newly presented and made of record.

Claims 1-3, 11, 14, 24-28, 34, 40, 46, 49-51, 53, 57, 59, 62, 64-67 and 74-76 are pending in the instant invention. Claims 1-3, 11, 14, 24-28, 34, 40, 46, 49, 51, 53, 57, 59, and 62 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 50, 64-67 and 74-76 are under consideration.

Priority:

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, provisional application 60/411,248, filed 17 September 2002, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The provisional application does not teach a method of inhibiting a cell cycle of a cell comprising administering a Nup153 inhibitor wherein the Nup153 inhibitor

comprises SEQ ID NO:30. Therefore, priority for claims 75 and 76 is granted to PCT/US03/29267, filed 17 September 2003.

Information Disclosure Statement:

The Information Disclosure statements (IDS) submitted on the 9 June 2008 has been considered. The signed copy is attached.

The listing of references in the specification, for example, pages 103-108, is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Withdrawn Rejections

The rejection of Claim 50 under 35 U.S.C. 112, second paragraph, is withdrawn in light of Applicants' amendment to the claim.

The rejection of Claim 50 under 35 U.S.C. 102(b) as being anticipated by Shah et al. is withdrawn, upon further consideration and in light of Applicants' persuasive arguments.

The rejection of Claim 50 under 35 U.S.C. 112, first paragraph, written description, is withdrawn upon further consideration and in light of Applicants' persuasive arguments.

Maintained/New Objections and/or Rejections

Objections

Title:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claims are drawn to a

method of inhibiting a cell cycle. The following title is suggested "Methods of inhibiting cell cycle of a cell comprising administration of a Nup153 inhibitor"

Sequence Rules:

The specification is not in compliance with the requirements of 37 CFR 1.821 through 1.825 of the Sequence Rules and Regulations. Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequences by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text or claims of the patent application.

37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amno acids or an unbranched sequence of ten or more nucleotides. Please see MPEP 2422.01

The specification discloses amino acid sequences in Figures 3, 9, 14 and 15. However, these sequences are not identified by sequence identifiers in the figures or in brief description of the figures.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.82(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03). **Compliance with the sequence rules is required**.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action

Rejections

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 50 and newly submitted claims 64-67 and 74-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting cell cycle of a cell *in vitro* comprising administering a Nup153 inhibitor to the cell, does not reasonably provide enablement for a method of inhibiting cell cycle of a cell *in vivo* comprising administering a Nup153 inhibitor to the cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a method of inhibiting a cell cycle comprising administering a Nup153 inhibitor to a cell. Given the broadest reasonable interpretation, the claims encompass administration of an inhibitor to an isolated cell, and to a subject comprising said cell (*in vivo* administration). The claims are also broadly drawn to a method of treating cancer in a subject.

The specification teaches a method of inhibiting a cell cycle of a cell comprising administering a Nup153 inhibitor to the cell in vitro [paragraph 0297 of PGPUB

20050226879, the PGPUB of the instant application]. The test system disclosed comprises cell free extracts derived from Xenopus eggs, which were used to form synthetic nuclei around sperm chromatin. When an inhibitor of Nup 153, a fragment encompassing the central zinc finger domain of Nup 153, was included in the cell free system, inhibition of nuclear envelope breakdown was apparent [paragraph 0038]. Antibodies that specifically recognize Nup153 were able to prevent the normal progression of events in nuclear envelope disassembly. The nuclear membrane stayed largely intact after administration of said antibodies to the cell free extracts [paragraph 0161]. The disclosure teaches that methods which inhibit nuclear envelope breakdown may inhibit cancer cell proliferation [paragraph 0026]. Methods of identifying compounds that inhibit nuclear envelope breakdown are taught [paragraphs 0267-0272]. The disclosure contemplates utilization of the identified compounds to treat a subject with cancer [paragraphs 0302-0304].

Working examples: Examples 1 and 2 teach incubation of Nup153 fragments (Example 1) or synthetic peptides (13-meres) (Example 2) with cell free extracts derived from *Xenopus* eggs; these extracts form synthetic nuclei around sperm chromatin. Administration of these inhibitors of Nup 153 inhibits the breakdown of the nuclear envelope. There are no teachings, working or prophetic, of administration of inhibitors of Nup153 *in vivo.*

Administration of a Nup153 inhibitor *in vivo* to inhibit cell cycle progression or to treat cancer is not enabled because the teachings in the specification provide insufficient guidance and objective evidence to predictably enable the use of the claimed methods *in vivo*. *In vitro* assays, as detailed in the disclosure of the instant application are useful in determining basic physiological phenomena and in screening the effects of potential therapeutic compounds. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the controlled conditions of an *in vitro* assay does not permit a single extrapolation of in vitro assays to human treatment efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Dermer (1994. Bio/Technology 12:320)

teaches that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. The reference teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. Dermer teaches that evidence of the contradictions between life in a Petri dish and in the body has been in the scientific literature for more than 30 years. It is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicated the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Additionally, the treatment of cancer in a subject is quite unpredictable as underscored by Gura (1997. Science 278:1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in vitro to in vivo protocols. The reference teaches that since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column), wherein the fundamental problem in drug discover for cancer is that the model systems are not predictive.

Due to the large quantity of experimentation necessary to determine if administration of Nup153 inhibitors in vivo would be effective in inhibiting cell cycle progression, and thus be effective in treating cancer in a subject, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of treatment of cancer in a subject and the breadth of the claims which fail to recite any limitations as to *in vitro*, undue experimentation would be required of the skilled artisan to practice the claimed invention in its full scope.

Applicants traverse the rejection (Response of 9 June 2008, page 9, last paragraph, bridging page 12, 1st paragraph). The reasons for the traversal are:

It was well established in the art that cell cycle progression can be stopped *in vivo* in order to inhibit the growth of cancer, for example. For example, the specification teaches that "Taxol a chemical derived from an extract of the yew tree, binds to the microtubules and does not allow them to disassemble. This causes the cells to fail in the mitosis process and die." (Specification, page 6, lines 7-12). One of ordinary skill in the art would have known that a wide variety of compounds exist that have been shown to inhibit cell cycle progression *in vivo,* and that the Nup153 inhibitors disclosed herein would have also been able to halt cell cycle progression *in vivo.*

Not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The Office Action asserts that due to the unpredictability of developing pharmaceutical therapies and the unpredictability of transferring nucleic acids into an organism's cell, undue experimentation would be necessary. However, there are multiple cell cycle inhibition therapies currently on the market which are effective in treating cancer, and applicants venture to assert that all, or nearly all, of these treatments were first tested *in vitro,* as is standard practice in the art.

Applicant's arguments have been fully considered but have not been found to be persuasive. Chemicals, such as Taxol, that bind to microtubules thereby inhibiting cell cycle progression are known to inhibit the growth of cancer in vivo. However, the fact that Taxol is effective *in vivo* is not predictive that an inhibitor of Nup153 would also be effective *in vivo*.

As discussed above, Applicants have only taught methods of inhibiting a cell cycle in a cell by administering a Nup 153 inhibitor to a cell extract and to cell culture systems, that is, *in vitro*. However, the narrowly defined and controlled conditions of an in vitro assay system does not permit a single extrapolation of in vitro assays to human

therapeutic efficacy with any reasonable degree of predictability. No model that can reasonably be correlated to the breadth of the claimed method has been presented.

With regard to the unpredictability of transferring nucleic acids into an organism's cell: while it is true that many clinical therapies for the effective treatment of cancer involve administration of drugs which inhibit the cell cycle of a cell, almost all of these therapeutic protocols involve the administration of small molecules such as flavopiridol, indisulam, AZD5438, SNS-032, bryostatin-1, seliciclib, PD 0332991, and SCH 727965 (Dickson et al. 2009. Current Oncology. 16:36-43, abstract). The Examiner is unaware of any clinical protocols that comprise administration of the functional nucleic acids disclosed in the specification of the instant invention. The art of record, as cited in previous Office Action, establishes the unpredictability of gene therapy protocols. Thus, one of ordinary skill could not practice the claimed invention commensurate with the full scope of the claims without undertaking undue experimentation.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 50 and 64-67 are rejected under 35 U.S.C. 102(a) as being anticipated by Harborth et al. (2001. J. Cell Sci. 114:4557-4565).

Harborth et al teach administration of siRNA duplexes to silence nuclear envelope proteins. Among the proteins silenced by administration of siRNA to HeLa cells (a cell line derived from cervical cells) was Nup153 (page 4560, 1st column, last paragraph), thus teaching an inhibitor of Nup153. The reference teaches that administration of siRNAs directed against Nup153 to HeLa cells resulted in cells which rounded up and showed growth arrest (page 4561, 1st column, 3rd paragraph). Thus, the teachings of Harborth et al anticipate all the limitations of claims 50, 64 and 67. One of ordinary skill in the art would recognize that a cell exhibiting growth arrest is arrested

in interphase and does not undergo mitosis; therefore the limitations of Claims 65 and 66 are also anticipated.

Therefore, the teachings of Harborth et al. anticipate all the limitations of Claims 50 and 64-67.

Conclusion:

No claims are allowed

In light of new grounds of rejection, this Action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shulamith H. Shafer/
Examiner, Art Unit 1647